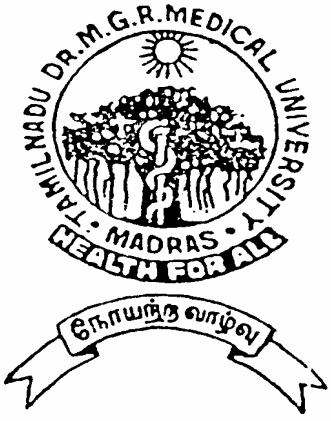
NUTRITIONAL ASSESSMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE

DISSERTATION SUBMITTED FOR

M.D DEGREE (Branch I) GENERAL MEDICINE



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CERTIFICATE

This is to certify that the dissertation titled **"NUTRITIONAL ASSESSMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE "** submitted by **Dr. ANEEB RAJ V.P.** to the Faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (General Medicine) is a bonafide research work carried out by him under our direct supervision and guidance.

Dr. MOSES K. DANIEL M.D.,
Addl.Professor of Medicine
Chief IV Medical Unit,
Department of Medicine,
Madurai Medical College,
Madurai.

Dr. A. AYYAPPAN M.D.,
Professor and Head
Department of Medicine,
Madurai Medical College,
Madurai.

DECLARATION

I, **Dr. ANEEB RAJ V.P**., solemnly declare that the dissertation titled "**NUTRITIONAL ASSESSMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE"** has been prepared by me.

This is submitted to the **Tamilnadu Dr. M.G.R. Medical University**, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Branch I (General Medicine).

Place : Madurai

Date : **Dr. ANEEB RAJ V.P.**

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CONTENTS

INTRODUCTION

Chronic kidney disease (CKD) is emerging as a global pandemic but it is a highly under recognized health problem in India .CKD ranks the 3rd amongst the leading life-threatening disease following cancer and cardiac ailments.[16]

March 9 is observed as World kidney day by the WHO to create awareness among the people about the magnitude of this deadly disease and start early treatment to reduce the mortality and morbidity from this disease.

Every 10th person is suffering from CKD and by this calculation we are having 100 millions people suffering from CKD in India.

Statistics have revealed a doubling of incidence in past few years[39] (US NHANES III 1988 to 94 - 3%).

Since CKD is often asymptomatic until End stage renal disease (ESRD) sets in, this estimation may only be akin to the tip of an iceberg

Increasing patient burden causes a considerable proportion of available healthcare resources to be spent on renal replacement therapy (RRT).

The enormous cost for dialysis and transplantation procedures post transplant medicines and the relative lack of technical centers providing these facilities is a big challenge before us.

Hence CKD has been globally recognized as a major economic and organizational concern.

CKD has been aptly mentioned as the “The Silent Killer”. In a developing country like ours we can ill afford the treatment of end stage renal disease and hence it is important for us to understand prevent and if not manage CKD well.

AIMS AND OBJECTIVES

1. To assess the nutritional status of patients with chronic kidney disease in and around Madurai.
2. To detect the incidence and nature of anemia in patients with chronic kidney disease.
3. To find out the prevalence of iron deficient state in patients with chronic kidney disease in comparison with normal controls.

REVIEW OF LITERATURE

Chronic kidney disease has become a global epidemic. Management of such a devastating disease is a highly complicated issue even among the well developed countries.

Medical, ethical, psychological and socio-economic problems associated with CKD is a large burden to the healthcare sector of the developing countries like India.

Definition of CKD: National Kidney Foundation(NKF) has defined CKD[16]

Criteria :

1. .Kidney damage > 3months ,either structural or functional abnormality with or without decreased glomerular filtration rate (GFR) ,manifested by either pathologic abnormalities or markers of kidney damage in blood, urine or imaging studies.

2.GFR < 60 ml/min /1.73 m2 > 3 months with or without kidney damage

Though many etiologies predispose to CKD the clinical consequences of renal failure are the same and ultimately contribute to the morbidity and mortality of the disease. The major consequence of CKD is premature death due to cardio vascular disease (CVD).[17,18] Recently revealing data have highlighted that even small increases in serum creatinine levels have a huge impact on cardiovascular mortality[19,20].

Causes of chronic renal failure:

Primary glomerulonephritis:

- Proliferative
- Focal glomerulosclerosis
- Membranous
- Membranoproliferative
- Crescentic

Secondary :

- Diabetes mellitus (DM)
- Systemic lupus erythematosus (SLE)
- Amyloidosis
- Vasculitis

Interstitial disease:

- Chronic interstitial disease
- Chronic pyelonephritis
- Reflux nephropathy

Hypertensive renal disease:

- Nephrosclerosis
- Renal artery stenosis

Obstructive uropathy:

- Urinary calculus disease
- Prostatic enlargement
- Tumors

Heredofamilial renal disease:

- Autosomal polycystic kidney disease (ADPKD)
- Medullary cystic renal disease
- Alports syndrome

Comparing the causes of ESRD allover the globe there is a striking difference between the western and Indian population. In the USA the leading cause of ESRD is diabetes mellitus , next being hypertension but in our country even though large scale data are not available the leading cause of ESRD is glomerulonephritis over diabetes and hypertension.

Other causes like interstitial nephritis, HIV nephropathy etc also forms a significant proportion of cases leading to ESRD.

STAGES OF CHRONIC KIDNEY DISEASE

Stage	Description	GFR (mL/min/1.73m2)	Action
1	Kidney damage with normal GFR	> 90	Diagnosis and treatment of comorbid condition, Slow progression, CVD risk reduction
2	Kidney damage with mild reduction of GFR	60 – 89	Estimating progression
3	Moderate reduction of GFR	30 – 59	Evaluate and treat complications
4	Severe reduction of GFR	15 – 29	Preparation for kidney replacement therapy
5	Kidney failure	< 15 or dialysis	Renal replacement therapy

Thus there is a need for early detection and treatment.

The significance of National kidney foundation – kidney disease outcome quality initiative (NKF-K/DOQI) staging :

- Shift of focus –GFR as the sole criteria for defining chronic renal disease to the identification of harbingers of early kidney damage including proteinuria, and abnormal urine sediment
- The concept of CKD with normal GFR but markers of kidney damage like persistent proteinuria is rewarding as an optimal treatment at this early stage may arrest the progression of illness.
- Hence they should form the main focus of preventive strategies. This staging helps to plan further treatment and predict outcome.

Malnutrition is an important consequence of CKD due to various reasons esp. the people on dialysis and caries a poor prognosis.

Protein-energy malnutrition (PEM) is very common among patients with advanced chronic renal failure (CRF) and those undergoing maintenance dialysis (MD) therapy worldwide. Different reports suggest that the prevalence of this condition varies from roughly 18% to 70% of adult MD patients. In adults, the presence of PEM is one of the strongest predictors of morbidity and mortality. However, in the poorly nourished pediatric patient, mortality is less common, and growth retardation is an

additional and greater concern. Impaired linear growth persists despite ongoing renal replacement therapy with either hemodialysis (HD) or peritoneal dialysis, and improvements in linear growth after successful renal transplantation usually fail to fully correct pre-existing growth retardation unless growth hormone (GH) is administered. Although several factors contribute to the impaired skeletal growth in pediatric patients with chronic renal disease, protein and energy malnutrition play a critical role, particularly during the first few years of life. Additional factors that contribute to impaired growth in pediatric patients include anemia, acidemia, calcitriol deficiency, renal osteodystrophy, and tissue resistance to the actions of GH and insulin-like growth factor-I (IGF-I

There are many causes of PEM in patients with advanced CRF.[1,4,7] These include:

(a) Inadequate food intake secondary to:

- Anorexia caused by the uremic state
- Altered taste sensation
- Intercurrent illness
- Emotional distress or illness

- Impaired ability to procure, prepare, or mechanically ingest foods
- Unpalatable prescribed diets

(b) The catabolic response to superimposed illnesses

(c) The dialysis procedure itself, which may promote wasting by removing such nutrients as amino acids, peptides, protein, glucose, water-soluble vitamins, and other bioactive compounds, and may promote protein catabolism, due to bioincompatibility

(d) Conditions associated with chronic renal failure that may induce a chronic inflammatory state and may promote hypercatabolism and anorexia

(e) Loss of blood due to:

- Gastrointestinal bleeding
- Frequent blood sampling
- Blood sequestrated in the hemodialyzer and tubing

(f) Endocrine disorders of uremia (resistance to the actions of insulin and IGF-1, hyperglucagonemia, and hyperparathyroidism)

(g) Possibly the accumulation of endogenously formed uremic toxins or the ingestion of exogenous toxins.

Serum Albumin[44,45,46]

The concentration of serum albumin has long been used as an index of protein nutrition, even though it responds relatively slowly to changes in protein stores because of a half-life of about 20 days. Hence, plasma albumin levels in malnourished patients are only slowly restored to normal during protein refeeding.[43] When hypoalbuminemia occurs in non-nephrotic CRF patients, it should be viewed as a sign of protein malnutrition.

There are, however, other factors that influence the albumin concentration. Kaysen and co-workers have emphasized that albumin synthesis falls sharply in subjects with inflammatory illnesses (i.e., albumin functions as a 'negative' acute phase reactant).[46,44,45] In studying the causes of hypoalbuminemia in dialysis patients, they found that there is a relationship between hypoalbuminemia and an inadequate diet, but they also noted that there is a relationship with higher serum levels of amyloid A and C-reactive protein, the acute-phase reactant proteins. Qureshi and associates found a relationship between hypoalbuminemia and higher levels of C-reactive protein, and noted that C-reactive protein levels were associated with malnutrition in their cross-sectional study of

hemodialysis patients.[61] It is not settled whether these relationships are nonspecific or whether they are related to inflammation associated with the dialysis treatment. Regarding the influence of nutritional factors, there is evidence that the serum albumin concentration is stable or even rises in patients with progressive renal insufficiency when they are receiving proper dietary instructions.[62,63-65]

Anthropometrics

Evaluation of abnormal anthropometry in CRF patients is complicated, because most reports are based on a single evaluation and the measurements are compared to those of normal healthy adults.[47] Moreover, the interpretation of abnormal values is questionable. For example, there are reports of normal values of serum proteins, even though anthropometric changes were compatible with loss of muscle mass.[48,49] Kopple[66] and Bergstrom[50] conclude that there is a high incidence of anthropometric abnormalities in virtually all cross-sectional studies of dialysis patients, suggesting malnutrition. This conclusion, plus the observation that the average protein intake of predialysis patients decreases with advancing renal insufficiency,[67] have led some to suggest that dialysis should be initiated early to avoid malnutrition and improve

the prognosis.[51,52] However, it is unlikely that anthropometric abnormalities can be generally attributed to low-protein diets prescribed during the predialysis period.[65] When predialysis patients were examined before and after 1 year of amino acid- and ketoacid-supplemented regimens, no decrease in nutritional status was seen, as indicated by changes in plasma proteins or anthropometry.[53,54] Similarly, long-term (6 to 72 months) observation of patients treated with the same supplements revealed normal values of serum albumin and transferrin.[63] The importance of anthropometrics in assessing the effectiveness of nutritional therapy is limited, especially if data are only from a single measurement in a cross-sectional analysis of nutritional status.

THE ANEMIA OF CHRONIC RENAL FAILURE

The anemia is a well known and major complication of CKD and is considered a hall mark of chronicity of renal disease.[1] It is multifactorial in origin even though traditionally considered as normocytic normochromic anemia due to erythropoetin deficiency other factors like iron deficiency contribute a major proportion and this is worsened in patients on dialysis and erythropoietin therapy

1. Decreased Erythropoietin production

a) Plasma erythropoietin (EPO) levels are inappropriately low for the degree of anaemia. The normal feedback mechanism operate poorly in increasing erythropoietin secretion.[1,3,7]

b) Oxygen dependency is still maintained but operates at a much lower level of sensitivity.[7]

c) Neocytolysis is a pathological process affecting selectively the young RBC's. EPO depression appear to initiate this process. Though the exact mechanism is unknown, it is postulated that endothelial cells secrete cytokines influencing adhesive interactions between young RBC's and reticulo endothelial phagocytes.[28]

2. Decreased Erythrocyte survival

a) Metabolic factors

i) Reduced HMP shunt activity renders cells sensitive to oxidative stresses.

ii) Hyperparathyroidism contribute to haemolysis by increasing red cell osmotic fragility.

iii) Use of immunohemolytic drugs like alphamethyldopa adds to the problems.[1,3,6]

b) Mechanical factors

Microangiopathic hemolytic anemia resulting from hypertension.[6,10]

c) Hypersplenism

Splenomegaly may occur secondary to marrow fibrosis, chronic hepatitis and transfusion hemosiderosis.[6]

3. Blood Loss

a. Chronic gastrointestinal and genitourinary loss
b. Dialyser loss
c. Loss from fistulae
d. Blood loss from repeated bleeding for investigations.

4. Platelet dysfunction

a) Defective function of Glycoprotiein Gp II b – III a complex.[21,20]
b) Functional defect in von willebrand factor VWF – platelet interaction
c) Increased prosta glandin ($PGI_{2)}$ secondary to hyperparathyroidism

d) Decreased granule content of Adenosine di phosphate (ADP).

e) Increased oxygen derived free radicals.

f) Reduced life - span of platelets due to reduced thrombopoietin.

5. Uremic inhibitors of erythropoiesis

The various uremic toxins postulated are [7,23,24]

a) **Byproducts of protein and aminoacid metabolism**

I. Urea – 80% of total excreted nitrogen.

II. Guanidine Compounds (Guanidine, methyl guanidine, Creatinine, Creatine etc).

III. Urates and hippurates.

IV. End products of aliphatic amine metabolism

V. End products of aromatic aminoacid metabolism (tryptophan, tyrosine, phenylalanine)

VI. Other nitrogenous substances (myoinositol, polyamines, phenols etc).

b. Advanced glycation end products

c. Inhibitors of ligand – protein binding

d. Glucurono conjugates and aglycones

e. Inhibitors of somatomedin and insulin action.

6. Aluminium toxicity

It occurs in patients on chronic haemodialysis patients and also with chronic use of aluminium hydroxide as phosphate binder. Aluminium inhibits erythropoiesis by interfering with iron transport and or its utilisation, inhibition of heme synthesis or increased hemolysis due to increased red cell fragility.[7,25,26]

7. Nutritional factors

Anorexia from uremia and various drugs and dietary restriction lead to iron deficiency and folate deficiency.[1,7]

8. Inflammation

The inflammatory mediators that are known to be in increased levels like cytokines Tumour necrosis factor-alpha and interferon gamma are also known to inhibit erythropoiesis.[78,79]

CORRECTABLE CAUSES OF ANAEMIA IN CRF[6]

Causes	Mechanism
1.Blood loss	a. Iatrogenic loss
	b. Dialyser loss
	c. Loss through fistula or shunt
	d. GI loss
2. Folate deficiency	a. Increased demand
	b. Restricted intake
	c. Dialyser loss
	d. Drugs
3. Acclerated Haemolysis	
i) Dialyser associated	a. Chemicals (copper, chloramines, formaldehyde, nitrates).
	b. Overheating of RBC's.
	c. Mechanical fragmentation of RBC's
	d. Dehydration or overhydration of RBC's

ii) Drugs	a. Oxidant drugs
	b. Immunohemolytic drugs like Alphamethyldopa.
iii) Microangiopathy	a. Hypertension
	b. Vasculitis
iv) Red cell phosphate	a. Excessive intake of antacids leading to deplet on.

PARAMETERS USED TO STUDY IRON STORES

1. Serum iron (SI)
2. Total iron binding capacity (TIBC)
3. Percentage saturation of transferrin (%) TSAT
4. Serum ferritin (SF)
5. Marrow sideroblasts.
6. Red cell protoporphyrin
7. Serum transferrin receptor (TfRC)

1. Serum iron

The serum iron level represents the amount of circulating iron bound to transferrin.

Normal range is 50-150 micrograms/dl.

2. **TIBC**

It is an indirect measure of circulating transferrin. The normal range is 300-360 micrograms/dl.

3. **Percentage saturation of transferrin. (TSAT)**

It is calculated using the formula

$$\frac{\text{Serum Iron}}{\text{TIBC}} \times 100$$

Normal transferrin saturation is 25-50%. Iron deficiency is associated with a saturation of <16%. A transferrin saturation of >50% indicates that a disproportionate amount of iron bound to transferrin is being delivered to non erythroid tissues.

4. **Serum ferritin**[1]

Serum ferritin exists in equilibrium with tissue stores of iron . The normal value of ferritin varies according to the gender.

Adult males have an average of 100 microgram/dl. Adult females have levels averaging 30 microgram/dl.

5. Estimation of bone marrow stores

This is the most accurate method of detecting iron stores.[6] However because it is invasive it has been replaced by the estimation of serum ferritin. The iron store measurements.

Iron Stores	Marrow iron stain (0-4+)	Serum Ferritin (Miccrogm/l)
0	0	<15
1-300mg	Traces to 1+	15-30
300-800mg	2+	30-60
800-1000mg	3+	60-150
1-2gms	4+	> 150
iron overload	-	> 500-1000

Marrow sideroblasts which normally constitute 40-60% have visible ferritin granules. In iron deficiency its value falls.

6. Red cell protoporphyrin levels

It is an intermediate in the pathyway of heme synthesis. Under conditions in which heme synthesis is impaired, protoporphyrin

accumulates within the red cell. This reflects an inadequate iron supply to erythroid precursors to support hemoglobin synthesis.

Normal values is less than 30 microgram/dl.

RBC INDICES

The red cell indices are calculated mean values that reflect the size, weight and haemoglobin (Hb) content of individual erythrocytes. They consist of

- Mean corpuscular volume (MCV)
- Mean corpuscular haemoglobin (MCH)
- Mean corpuscular haemoglobin concentration (MCHC).

MCV – indicates volume of Hb in each cell.

MCH – indicates weight of Hb in each cell

MCHC – indicates the proportion of haemoglobin contained in each red cell.

Using the red cell indices anaemias are classified as

ANAEMIA	MCV (fl)	MCH (pg)	MCHC (%)
Normal	90±9	32±2	33±3
Hypochromic microcytic	50-80	12-25	25-30
Normochromic microcytic	<80	20-25	<27
Normochromic macrocytic	95-150	30-50	32-36
Normochromic normocytic	82-92	25-30	32-36

STAGES OF IRON DEFICIENCY ANAEMIA

Iron deficiency anaemia is the condition in which there is anaemia and clear evidence of iron deficiency. However it is worthwhile to consider the steps by which iron deficiency anaemia occurs. It can be divided into three stages.[3,9]

a. Stage of prelatent iron deficiency or iron depletion[2,3]

This represents a reduction in iron stores without reduced serum iron levels. This stage is usually detected by a low serum ferritin level. Latent iron deficiency is said to exist when iron stores are exhausted, but the blood hemoglobin level remains higher than the lower limit of normal.

b. Stage of iron deficient erythropoiesis

In this second stage, certain biochemical abnormalities of iron – limited erythropoiesis may be detected, including reduced transferrin saturation, increased TIBC, increased free erythrocyte protoporphyrin, increased zinc protoporphyrin, and increased serum TfRC. Other findings include subnormal urinary iron excretion after deferoxamine injection and decreased tissue cytochrome oxidase levels. The mean corpuscular volume usually remains within normal limits, but a few microcytes may be detected on a blood smear. Many patients report generalized fatigue or malaise, even though they are not yet anemic.

c. Stage of iron deficient anaemia

In this stage the blood hemoglobin concentration falls below the lower limit of normal, and iron deficiency anemia is apparent. Iron-containing enzymes, such as the cytochromes, also reach abnormally low levels during this period. This stage is characterized by hypochromic, microcytic cells, TIBC increases, percentage saturation is much less and a very low levels of serum ferritin.

Stages in the Development of Iron Deficiency[2]

	Stage 1 (Prelatent)	Stage 2 (Latent)	Stage 3 (Anemia)
Bone marrow iron	Reduced	Absent	Absent
Serum ferritin	Reduced	<12 μg/L	<12μg/L
Transferrin saturation	Normal	<16%	<16%
Free erythrocyte protoporphyrin, zinc protoporphyrin	Normal	Increased	Increased
Serum transferrin receptor	Normal	Increased	Increased
Reticulocyte hemoglobin content	Normal	Decreased	Decreased
Hemoglobin	Normal	Normal	Reduced
Mean corpuscular volume	Normal	Normal	Reduced
Symptoms	Fatigue, malaise in some patients		Pallor, pica, epithelial changes

Iron deficiency

A suboptimal response to recombinant human erytheropoietia (rhEPO) most commonly results from failure of delivery of an adequate amount of iron to the erythron. Enhanced iron utilization due to rhEPO-

induced red blood cell formation can quickly deplete iron stores previously reduced by poor iron absorption, occult gastrointestinal bleeding, or dialysis-related blood losses.[68] Treatment with rhEPO is, at this time, the most common cause of iron deficiency. Most treated patients become iron deficient[69] and therefore require more rhEPO to maintain the same rate of RBC production. If the iron balance is not restored by oral or parenteral iron replacement and iron deficiency worsens, an initial good response may then falter. The most accurate assessment of the iron stores is given by staining the bone marrow aspirate for iron with Perl's Prussian blue stain.[70]

In the lack of this reliable, but invasive, reference standard, the iron status is commonly assessed by serum iron concentration, serum ferritin (SF), transferrin saturation (TfS), and RBC indices.[68] Serum iron concentration fluctuates during rhEPO administration, but SF, a protein secreted into the plasma by the reticuloendothelial cells under the regulation of intracellular iron concentration, is a good indicator of iron stores[71]; TfS index (calculated according to the formula: saturation % = serum iron/total iron capacity)–that means the transferrin-bound iron–appears to be even better (higher sensitivity and similar specificity).[70] Iron

deficiency secondary to the consumption of iron deposits by rhEPO-stimulated erythropoiesis may be concealed by the persistence of apparently adequate ferritin levels, but it is disclosed by both a TfS level less than 20% and prompt erythropoietic response to intravenous administration of iron dextran. In a study on the early predictors of a response to rhEPO, the initial values of serum iron, TfS, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) were significantly lower in the iron-responsive group than in the iron-nonresponsive one; furthermore, there was a strong inverse relationship between initial TfS and the change in hematocrit following iron therapy in patients hyporesponsive to rhEPO.[72] The failure to make enough iron available to meet the demands of enhanced erythropoiesis despite the presence of adequate iron stores, as reflected by the level of SF, has been defined as ‘functional iron deficiency’ (compared to absolute iron deficiency’ or ‘iron storage deficiency’). The red blood cells appear hypochromic (with MCHC <28 g/dL) when mobilization of iron from stores and its transport to the erythron become inadequate. A percentage of circulating hypochromic red blood cells greater than 10% (normal range: <2.5% of circulating red cells), in the presence of adequate iron

stores and the absence of hemoglobinopathies or inflammatory diseases, should be diagnostic of functional iron deficiency.[73,74] Other more sophisticated tests for iron deficiency have been proposed: erythrocyte ferritin[75,76] ; hemoglobin content of reticulocytes (CHr); free erythrocyte protoporphyrin (FEP); and serum transferrin receptors (TfRC). A reduced erythrocyte ferritin level despite normal SF should suggest functional iron deficiency, a condition that measurement of both CHr and erythrocyte ferritin could help identify.[77]

Chronic renal failure patients treated with hemodialysis [80,81]

Iron deficiency affects a significant fraction of patients treated with hemodialysis when transfusions are restricted [84]. Absolute iron deficiency may result from the loss of blood associated with the dialysis process and diagnostic tests. Gastrointestinal blood losses may also be substantial, averaging 6.27ml/day in one study [44]. Telangiectasias are among the most common bleeding gastrointestinal lesions in patients with renal failure[2].

Iron kinetics in the non – dialyzed CRF patients

In CRF, progressive renal insufficiency leads to increasing anaemia.

The anaemia is generally normochromic normocytic in nature due to hypoproliferation of bonemarrow. The iron profile values like serum iron, iron binding capacity, serum ferritin, percentage saturation of iron transferrin saturation, free erythrocyte protoporphyrin, zinc protoporphyrin, serum transferrin receptor and reticulocyte hemoglobin content are also within normal limits. However in any population where iron deficiency occurs due to various reasons, low iron profile or a microcytic hypochromic anaemia may occur[7].

Pitfalls in iron profile studies in renal failure [82,84]

In renal failure various pathogenic factors are in play. These include inflammatory and humoral factors[84].

These factors increase the levels of various reactive proteins of which transferrin is also one[80]. This may give rise to elevated levels of serum iron but with decreased saturation of transferrin. Hence serum iron is not an accurate predictor.

Some authors have demonstrated low serum iron levels due to reactive low iron concentration and the low iron levels corresponded with the serum ferritin level. However the results have been inconsistent and so serum iron is not a reliable guide to evaluate iron status. [27,28]

Serum Ferritin [84,77,75]

It is frequently used to assess the iron stores for the purpose of ensuring their adequacy for erythropoiesis[71]. However measurable ferritin may be increased when tissue ferritin is released during cellular injury. Erythropoiesis blockade can increase the iron pool elevating serum ferritin levels despite suppressed erythropoiesis[83].

Percentage saturation of iron (SI)

It is a very reliable parameter that gives an indication of the iron in the metabolic pool. Together with serum ferritin, it is taken to assess the iron parameters in haemodialysis patients.

The National kidney foundation – disease outcome quality initiative has postulated that saturation <20% and ferritin <100 μg/L indicates decreased iron pools[33].

MANIFESTATIONS OF ANEMIA IN CRF

1. The various signs and symptoms of anaemia namely tiredness, lethargy, fatigue, breathlessness at rest or on exertion, angina, palpitations, increased cold sensitivity, anorexia, loss of libido, menstrual irregularity, pallor, increase in heart rate, decreased cognition are present[24].

2. Anemia predisposes to bleeding diathesis. This feature is poorly understood[21].
3. There is increased cardiac output, peripheral vasodilatation and increase in LV mass all of which lead to left ventricular failure in later stages[23].
4. Anemia leads to myocardial ischemia and angina.

FUNCTIONAL CONSEQUENCES OF ANEMIA IN CRF

1. Impaired cognitive capability

Patients on dialysis are at a disadvantage of developing dementia due to many causes. Iron deficiency aggravates the problem.

2. Impaired exercise capacity

The exercise intolerance due to anaemia significantly increases the morbidity and impairs the quality of life.

3. Cardiac death [17,18]

The physiological response to anaemia are high stroke volume and an excess of catecholamines and non catecholamines due to chemoreceptor mediated increase in sympathetic activity.

Early myocardial changes are reversible if intervened effectively. But the late changes which include intense interstitial fibrosis and the

diastolic dysfunction of the heart are irreversible[19,20]. The vascular changes in CRF is arterial remodelling leading to thickening of aorta and stiffening. The altered systolic pressure and high inertia due to higher blood mass in the dilated arterial system contribute to the development of LVH and abnormal coronary perfusion. All these adverse changes lead to increase the rate of cardiac deaths in CRF.

FACTORS AFFECTING PREVALENCE OF ANAEMIA IN CRF[28]

1. Severity of renal dysfunction

There is a good correlation between the values of urea and creatinine and the quantity of hemoglobin.

2. Type of Dialysis

Hemodialysis leads to more iron loss than peritoneal dialysis

3. Trace element deficiencies

4. Aluminium toxicity

5. Folate and B_{12} deficiency

PRECIPITATION OF IRON DEFICIENCY ANAEMIA BY EPO[22,30,31]

EPO is used increasingly in the management of anaemia in CRF. The administration of EPO will lead to rapid depletion of the remaining iron stores and will precipitate iron deficiency anaemia[35].

IMPORTANCE OF DETECTING IRON DEFICIENCY ANAEMIA IN CRF

Most of the morbidity in CRF is due to anaemia to which iron deficiency is an important contributor. So identification and correction of iron deficiency anaemia improves the quality of life of CRF patients[33]. Also presence of iron deficiency leads to decrease in the effect of erythropoietin. Hence prompt recognition and proper correction of iron deficiency in CRF patients gains value[30].

EVALUATION OF IRON DEFICIENCY ANAEMIA IN CRF [29]

The (NKF) has formulated guidelines for the evaluation of iron parameters and treatment in dialysed patients, among other parameters to assess the adequacy of dialysis[33,16].

GUIDELINES FOR ANEMIA OF CHRONIC KIDNEY DISEASE

GUIDELINE 1

An anemia work-up should be initiated in patients with chronic kidney disease (CKD) when the:

• Hb <11g/dL (Hematocrit (Hct) is <33%) in pre-menopausal females and pre-pubertal patients

• Hb <12g/dL (Hct is <37%) in adult males and post-menopausal females

GUIDELINE 2

Anemia evaluation

A. Evaluation of anemia should consist of measurement of at least the following:

- Hemoglobin (Hb) and/or Hematocrit (Hct)
- Red blood cell (RBC) indices
- Reticulocyte count
- Iron parameters:
    - Serum iron
    - Total iron binding capacity (TIBC)

- Percent transferrin saturation (serum iron × 100 divided by TIBC) [TSAT]
- Serum ferritin

• A test for occult blood in stool

• B. This work-up should be performed before Erythropoietin therapy is begun.

GUIDELINE 3

Erythropoietin deficiency

If no cause for anemia other than CKD is detected, based on the work-up outlined in Guideline 2: Anemia evaluation, and the serum creatinine is >2 mg/dL, anemia is most likely due to EPO deficiency.

GUIDELINE 4: (Target Hct/ Hb for EPO therapy)

The target range for Hct (Hb) should be 33% (11g/dL) to 36% (12g/dL). This target is for EPO therapy and is not an indication for blood transfusion therapy.

III. Iron Support

Iron is essential for hemoglobin formation, as is erythropoietin. Several important issues related to iron deficiency and its management in the CKD patient, particularly in patients receiving Erythropoetin therapy should be considered:

1. Iron (blood) losses are high, particularly in the patients undergoing hemodialysis .
2. Oral iron usually cannot maintain adequate iron stores, particularly in the hemodialysis patients treated with EPO.
3. EPO, by stimulating erythropoiesis to greater than normal levels, often leads to functional iron deficiency.
4. Prevention of functional (and absolute) iron deficiency by regular use of intravenous iron (ie, small doses, weekly, to replace predicted blood losses) improves erythropoiesis.
5. The serum iron, total iron binding capacity, and serum ferritin are the best indicators of iron available for erythropoiesis and iron stores, but they do not provide absolute criteria for either iron deficiency or iron overload.

These guidelines suggest that the regular use of small doses of iv iron, particularly in the hemodialysis patient, will prevent iron deficiency and promote better erythropoiesis than can oral iron therapy.

GUIDELINE 5

Assessment of Iron status

Iron status should be monitored by the percent transferrin saturation (TSAT) and the serum ferritin. [36,37,71,75,77]

GUIDELINE 6

Target iron level

A. CKD patients should have sufficient iron to achieve and maintain an Hgb/Hct of 11 to 12 g/dL/33% to 36%.

B. To achieve and maintain this target Hgb/Hct, sufficient iron should be administered to maintain a TSAT of $\geq$20%, and a serum ferritin level of $\geq$100 ng/mL .

C. In hemodialysis patients in whom TSAT is $\geq$20% and the serum ferritin is $\geq$100 ng/mL, yet the Hgb/Hct is 11 g/dL/<33%, as well as in patients requiring comparatively large doses of erythropoietin to maintain an Hb/Hct of 11 to 12 g/dL/33% to 36%, the patient's response to 1.0 g of

iv iron given over 8 to 10 weeks should be observed. If in response to this course of iron, there is no increase in Hb/Hct and no increase in serum ferritin and TSAT level, at the same dose of EPO a second course of iv iron should be tried. If, in response to this second course of iv iron, there still is no increase in Hb/Hct, but either the TSAT or serum ferritin level increases, then the weekly dose of iv iron should be reduced to the lowest amount required to maintain the TSAT $\geq$20% and serum ferritin at $\geq$100 ng/mL. If, on the other hand, in response to either of these courses of iv iron, there is an increase in Hb/Hct at a constant dose of EPO, or a stable Hct at a decreased dose of EPO, then it is reasonable to administer 1.0 g of iron iv over 8 to 10 weeks again in an effort to achieve and maintain the Hb/Hct at 11 to 12 g/dL/33% to 36%.

D. CKD patients are unlikely to respond with a further increase in Hb/Hct and/or a further reduction in EPO dose required to maintain a given Hb/Hct if the TSAT increases to $\geq$50% and/or the serum ferritin level increases to $\geq$800 ng/mL.

Fernandez – Roudriguez et al have studied 63 patients with chronic renal failure undergoing dialysis and have concluded that serum ferritin

may be the most reliable parameter and saturation index is not a reliable parameter for diagnosing iron deficiency[34].

Milman W, Bangawell S et al who studied 50 non dialysis patients and 53 controls, have also predicted serum ferritin as a useful indicator of marrow iron stores in patients, with renal failure[38].

STUDY DESIGN

This study was conducted at Government Rajaji Hospital between period of June 2006 to March 2007.A total of 43 patients who were diagnosed to have Chronic kidney disease who were undergoing conservative management were enrolled into the study. Serum ferritin assay in subjects and controls using ELISA method were done at the Department of Biochemistry, Madurai Medical College. The study was approved by the Ethical committee, Government Rajaji Hospital. An informed consent was obtained from all study participants.

Nature of Study: Analytical Study,

Sample Size - 43

MATERIALS AND METHODS

Materials:

43 patients from medicine wards and nephrology ward

Diagnostic criteria:

1. Bilateral contracted kidneys
2. GFR <60 mL/min/1.73m_2.

Exclusion criteria:

Conditions that may alter the iron profile and RBC morphology were excluded on the basis of detailed history and clinical examination and basic investigations

They include:

1. All female patients
2. Chronic infections like tuberculosis, rheumatoid arthritis
3. Malignancies
4. Hemoglobinopathies
5. Bleeding disorders
6. Nephrotic syndrome
7. Chronic liver disease
8. HIV infection

9. Malabsorption
10. Steroid therapy
11. Patients receiving EPO therapy

Methods: A proper medical history from the patients were obtained which included the past history of diabetes mellitus, family history of renal disease, hypertension, coronary artery disease, drug history including nephrotoxic drugs, intercurrent illness and dietary habits

Clinical examination included:

1. Weight ,height body mass index (BMI) ,mid arm circumference (MAC)
2. Vital parameters
3. Major systems examination

Hematological investigations:

Hemoglobin , peripheral smear TC DC platelet count

Biochemical investigations:

Blood sugar

Renal parameters (blood urea serum creatinine)

Total proteins and serum albumin

Urine spot protein creatinine ratio

Serum ferritin : The serum ferritin was determined by using UBI – MAGIWEL ferritin kit (United biotech Inc California USA) by enzyme linked immunosorbent assay (ELISA using Robanik easy ELISA reader)

Ethical committee approval : Obtained

Consent : Informed consent was obtained

Financial support : Nil

Conflict of interest : Nil

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002).

Using this software, frequencies, percentage, mean, standard deviation, x^2 and 'p' values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

A. Characteristics of cases included in the study

Table 1

Distribution of patients in relation to age

Age group	Study cases	
	No.	%
Below 30	4	9.3
30-39	3	7
40-49	10	23.3
50-59	18	41.9
60 & above	8	18.6
Total	43	100
Mean	49.8 yrs	
S.D.	12.1 yrs	

Among the 43 male patients enrolled in the study the mean age was 49.8. The patients between the 3rd and 7th decade form the major number of the study.

Table 2

Risk Factors

Risk factor	Present		Absent	
	No.	%	No.	%
Diabetes	3	7	40	93
Hypertension	12	27.9	31	12.1
Smoking	15	34.9	28	65.1
B.P.	30	69.8	13	30.2
LVH	12	27.9	31	72.1

Assessing the risk factors of CKD in our patients it was found that diabetes mellitus contributed to only a meagre 7% of our patients. Significant history of hypertension was present in about 28% of our study group which may be either the cause or effect of CKD . Prevalence of smoking was present in about 35% of our patients. 70% of our study group were hypertensives at the time of diagnosis and out of them 28 % had LVH by ECG criteria, which is a significant risk factor for coronary artery disease. In our population apart from diabetes and hypertension

other causes of CKD are predominant especially in the young like primary glomerulonephritis, interstitial nephritis and so on.

Table 3
Mean values of baseline parameters

Parameter	Mean	S.D.
Weight	50.8 kg	8.1 kg
Height	161 cm	7 cm
BMI	19.56	2.78
MAC	21.6	1.8
Hb	7.04	1.93
PCV	21.8	6
Urea	156	61.6
Serum creatinine	7.35	4.19
Total protein	6.48	0.81
Albumin	3.28	0.41
GFR	11.5	6.21
Ferritin	86.9	70.9

In our study group the mean body mass index (BMI) of the patients was 19.56, which was low normal. Mid arm circumference also was less

for the age. (mean 21.6 cm). All the patients in our study were anemic with a mean Hb of 7.04 g/dl. Hypoalbuminemia was highly prevalent in our patients (mean – 3.28g/dl). The mean GFR of our patients were 11.5 ml/mt. Most of our patients came under the stage 4 and 5 of CKD staging and has either dialysis or transplant as their treatment option. Serum ferritin was also far below the recommended value in patients with CKD by NKF guidelines (>100 mcg/l).

Table 4

C.K.D Stage and cases

C.K.D. Stage (ml/mt/1.73mt^2)	**Study Cases**	
	No.	**%**
Stage I (GFR $\geq$ 90)	-	-
Stage II (GFR 60-89)	-	-
Stage III (GFR 30-59)	-	-
Stage IV (GFR 15-29)	12	27.9
Stage V (GFR < 15)	31	72.1
Total	43	100

Most of our patients were ESRD patients

Table 5

Type of peripheral smear (PS)

PS Type	Study Cases	
	No.	**%**
Microcytic Hypochromic (MC)	13	30.2
Dimorphic anaemia (DA)	17	39.6
Normocytic normochromic (NA)	13	30.2
Total	43	100

Microcytic hypochromic anemia was present in about 30% of our group. Normocytic normochromic anemia was seen in about 30% of the population. The remainder had dimorphic anemia.

B. Relationships between parameters and GFR and ferritin

Table 6

Age and GFR and serum ferritin

Age Group	GFR		Serum Ferritin	
	Mean	**S.D.**	**Mean**	**S.D.**
Below 30	5.29	0.57	30.75	18.14
30-39	5.97	1.6	125.33	78.27
40-49	11.37	6.12	76.3	83.03
50-59	13.98	6	77.61	69.14
60 & above	11.27	6.61	84.63	66.84
'p'	**0.0198** **(Significant)**		0.3137 (Not significant)	

Age and GFR have statistically significant relationship. No such relationship exists between age and ferritin.

Table 7

Relationship between BMI and GFR and serum ferritin

BMI	GFR		Serum Ferritin	
	Mean	**S.D.**	**Mean**	**S.D.**
Underweight (<18.5)	10.6	6.39	87.69	71.02
Normal (18.5 –24.9)	12.42	6.22	75.56	70.79
Overweight (25-30)	7.15	2.46	22	2.83
Obese (> 30)	-	-	-	-
'p'	0.4093 (Not significant)		0.2151 (Not significant)	

BMI has got no statistically significant relationship with GFR and ferritin.

Table 8

Relationship between C.K.D Stage (GFR) and Mid arm circumference (MAC)

C.K.D. Stage ($ml/mt/1.73mt^2$)	MAC	
	Mean	**S.D.**
Stage I (GFR $\geq$ 90)	-	-
Stage II (GFR 60-89)	-	-
Stage III (GFR 30-59)	-	-
Stage IV (GFR 15-29)	22.26	1.67
Stage V (GFR < 15)	21.35	1.81
'p'	0.2376 (Not significant)	

CKD stage does not affect MAC values significantly.

Table 9

Relationship between C.K.D Stage (GFR) and Anemia (Hb)

C.K.D. Stage (ml/mt/1.73mt^2)	**Hb**	
	Mean	**S.D.**
Stage I (GFR $\geq$ 90)	-	-
Stage II (GFR 60-89)	-	-
Stage III (GFR 30-59)	-	-
Stage IV (GFR 15-29)	8.96	1.76
Stage V (GFR < 15)	6.3	1.43
'p'	**0.0001 (Significant)**	

As CKD stage increases Hb levels decrease. This relationship is statistically significant.

Table 10

Relationship between CKD stage and PCV, urea and Sr. creatinine

CKD Stage (ml/mt/1.73mt^2)	PCV		Urea		Sr Creatinine	
	No.	%	No.	%	No.	%
Stage I (GFR $\geq$ 90)	-	-	-	-	-	-
Stage II (GFR 60-89)	-	-	-	-	-	-
Stage III (GFR 30-59)	-	-	-	-	-	-
Stage IV (GFR 15-29)	27.38	5.09	104.36	40.49	3.09	0.57
Stage V (GFR < 15)	19.65	4.88	176	56.78	9	3.79
'p'	**0.0002 (Significant)**		**0.0004 (Significant)**		**0.0001 (Significant)**	

As CKD stage increases, packed cell volume (PCV) levels decrease and urea and serum creatinine values increase. These relationships have got statistical significance.

Table 11

Relationship between CKD stage and Total protein and Albumin

CKD Stage (ml/mt/1.73mt^2)	Total Protein		Albumin	
	Mean	**S.D.**	**Mean**	**S.D.**
Stage I (GFR $\geq$ 90)	-	-	-	-
Stage II (GFR 60-89)	-	-	-	-
Stage III (GFR 30-59)	-	-	-	-
Stage IV (GFR 15-29)	6.34	0.88	3.28	0.57
Stage V (GFR < 15)	6.53	0.78	3.29	0.33
'p'	0.5238 (Not Significant)		0.9132 (Not Significant)	

There is no statistically significant relationship between CKD Stage and the values of total protein and albumin.

Table 12

Relationship between Left ventricular hypertrophy (LVH) and GFR and Sr. Ferritin

LVH	GFR		Sr. Ferritin	
	Mean	**S.D.**	**Mean**	**S.D.**
Present (12)	9.73	5.19	49.75	36.3
Absent (31)	12.19	6.51	88.35	76.69
'p'	0.2554 (Not significant)		0.1551 (Not significant)	

GFR and Ferritin values are not significantly affected by the presence or absence of LVH.

Table 13

PS and GFR and Sr. Ferritin

PS	GFR		Sr. Ferritin	
	Mean	**S.D.**	**Mean**	**S.D.**
Microcytic hypochromic (MC - 13)	9.94	5.27	23.15	8.58
Dimorphic (DA - 17)	11.03	6.55	88.53	78.02
Normocytic Normochromic (NA - 13)	13.68	6.47	117.69	60.62
'p'	0.2369 (Not significant)		**0.0001 (Significant)**	

There is statistically significant relationship between ferritin values and type of PS. No such relationship exists in the case of GFR values and PS type. Serum ferritin values were very low in patients with microcytic hypochromic anemia

Table 14

Comparison of serum ferritin values in cases and controls

Group	Serum Ferritin	
	Mean	**S.D.**
Study cases	77.58	69.67
Controls	108.11	70.98
'p'	**0.029 (Significant)**	

The mean ferritin values of the study cases are significantly lower than that of the controls.

Table 15

Relationship between stage of CKD and serum ferritin

CKD Stage (ml/mt/1.73mt^2)	**Serum Ferritin**	
	Mean	**S.D.**
IV (GFR 15-29)	97.7	89.8
V (GFR< 15)	69.8	60.1
'p'	**0.507 (not Significant)**	

No statistically significant relationship was observed between GFR and serum ferritin values.

Table 16

Comparison of total protein values in study and control groups

Group	Total protein	
	Mean	**S.D.**
Study	6.48	0.8
Control	6.12	0.5
'p'	**0.1344 (not Significant)**	

Serum total proteins were not significantly lesser in patients with CKD

Table 17

Serum albumin values in study and control groups

Group	Serum albumin	
	Mean	**S.D.**
Study	3.28	0.41
Control	4.33	0.25
'p'	**0.0001 (Significant)**	

Serum albumin showed a marked reduction in patients with CKD when compared to the normal controls

Table – 18

Distribution of BMI values in cases

BMI (kg/m^2)	Cases	
	No.	%
Underweight (<18.5)	16	37.2
Normal (18.5 –24.9)	25	58.1
Overweight (25-30)	2	4.7
Obese (> 30)	-	-
Total	43	100

About 37% of the total CKD patients were underweight (BMI<18.5)

Table – 19

Relationship between BMI and Serum Albumin

BMI (kg/m^2)	Serum Albumin	
	Mean	**S.D.**
Underweight (<18.5)	3.34	0.33
Normal (18.5 –24.9)	3.26	0.46
Overweight (25-30)	3.3	0.42
Obese (> 30)	-	-
Total	3.28	0.41
'p'	0.6819 (Not significant)	

There was no statistically significant relationship between nutritional parameters of BMI and serum albumin.

Table 20

Relationship between C.K.D Stage (GFR) and BMI

C.K.D. Stage (ml/mt/1.73mt^2)	BMI	
	Mean	S.D.
Stage I (GFR $\geq$ 90)	-	-
Stage II (GFR 60-89)	-	-
Stage III (GFR 30-59)	-	-
Stage IV (GFR 15-29)	19.84	1.94
Stage V (GFR < 15)	19.45	3.06
'p'	0.4323 (Not significant)	

No significant relationship was seen between GFR and BMI

Table 21

Comparison BMI values in cases and controls

Group	BMI	
	Mean	S.D.
Study cases	19.56	2.78
Controls	23.4	2
'p' value	0.0001 (Significant)	

The mean BMI of the study cases are significantly lower than that of the normal controls.

DISCUSSION

The dawn of 21st century has witnessed the emergence of chronic kidney disease as a global pandemic due to increasing incidence of predisposing factors like hypertension diabetes etc with an incidence of 6% in adult population

In patients with chronic kidney disease anemia and protein malnutrition are the two important predictors of mortality and morbidity

Numerous studies have demonstrated disorders of protein metabolism in uremia. Many of the abnormalities in protein metabolism associated with chronic renal failure persist in patients undergoing hemodialysis. The quantities of various essential and nonessential amino acids and their various ratios are altered in plasma,[56,57] muscle,[58] and red blood cells.[59] In addition, the turnover of albumin is altered, which, along with many other factors, contributes to a decrease in the serum albumin concentration in dialysis Patients.[57,60]

Serum albumin levels have been used extensively to assess the nutritional status of individuals with and without chronic renal failure (CRF). [85,86,76] Malnutrition is common in the end-stage renal disease (ESRD) population, and hypoalbuminemia is highly predictive of future

mortality risk when present at the time of initiation of chronic dialysis as well as during the course of maintenance dialysis (MD).[85-88] It follows that nutritional interventions that maintain or increase serum albumin concentrations may be associated with improved long-term survival, although this has not been proven in randomized, prospective clinical trials. Serum albumin levels may fall modestly with a sustained decrease in dietary protein and energy intake and may rise with increased protein or energy intake. Conversely, serum albumin levels may fall acutely with inflammation or acute or chronic stress and increase following resolution or recovery[44,45].

Although no single ideal measure of nutritional status exists, the serum albumin concentration is considered to be a useful indicator of protein-energy nutritional status in MD patients [91,94,95]. The extensive literature, in individuals with or without renal failure, relating serum albumin to nutritional status, and the powerful association between hypoalbuminemia and mortality risk in the MD population, strongly support this contention. In addition, the measurement of serum albumin levels is inexpensive, easy to perform, and widely available.

The progressive reduction in voluntary protein intake observed as patients approach end-stage renal failure, considered in light of the increasing prevalence of hypoalbuminemia with its attendant ominous implications for dialysis patients,[55] has led to the suggestion that increasing protein intake can prevent complications.[52,90,92] However, the inference that encouraging a high-protein diet will counteract hypoproteinemia is not borne out by experimental evidence[90]. on the contrary, a protein-restricted diet, including those supplemented by essential amino acids, improves protein nutrition while

ameliorating uremic symptoms, whereas a more "nearly normal" diet has the opposite effects. Thus, hypoalbuminemia can be prevented by prescribing a well- designed, low-protein diet. The suggestion that such diets will induce protein malnutrition has been repeatedly disproven. The largest study of this question, the Modification of diet in renal disease (MDRD) study, established unequivocally that low-protein diets as well as supplemented very-low-protein diets are nutritionally safe [89]

Anemia of chronic kidney disease is multifactorial in orgin whatever be the cause it is directly associated with increased mortality from cardiac diseases

The renal community has long recognized that anaemia can impair the quality of life of patients and lead to irreversible cardiac consequences. Anaemia, which occurs frequently and is often neglected, appears to precede left ventricular hypertrophy and CHF in renal transplant patients. Anaemia may not be an 'innocent bystander' in chronic disease;Anemia, an easily reversible feature of end-stage renal disease, is an independent risk factor for clinical and echocardiographic cardiac disease, like left ventricular dilatation as well as mortality in end-stage renal disease patients [17-20].

Available evidence demonstrates that:

Both iron and erythropoietin are needed to produce red blood cells; as a result, unless adequate iron is available, Erythropoietin will be relatively ineffective [28,30].

Although no tests are perfect indicators of the adequacy of iron stores, the TSAT and serum ferritin are the best measures of the body's iron status that we currently have. The probability that iron deficiency is present increases as the values of these measures decrease [34-36,41,42].

Given the prevalence of iron deficiency in CKD patients, and the sensitivity and specificity of TSAT and serum ferritin in detection of iron deficiency, the likelihood of iron deficiency is sufficiently high when TSAT is <20% and the serum ferritin is <100 ng/mL. Therefore, the TSAT and serum ferritin should be maintained at a level of ≥20% and ≥100 ng/mL, respectively, in all patients [33].

This study was undertaken with the aim of identifying the prevalence of iron deficient anemia in patients with chronic kidney disease and also the prevalence of protein energy malnutrition

Among the 43 male patients selected for the study the mean age of the study group was 49.8yrs In assessing the risk factors of chronic kidney disease in our patients the incidence of diabetes was only found to be 7% meanwhile 27.9% of the population had history of hypertension. This points to the fact that in our part of the world diabetes is not the prime cause of CKD. The various other causes like glomerulonephritis interstitial nephritis, analgesic nephropathy etc may be the leading cause of CKD and ESRD.

About 35% of the population of the patients were chronic smokers, which is also an important risk factor for progressive decline in GFR and ESRD.

At the time of presentation about 70% of the patients were hypertensives and among them about 28% had left ventricular hypertrophy by ECG criteria. These two form the major risk factors for cardiovascular death in patients with CKD

Anthropometric measurements were taken in patients, which included weight, height, body mass index, and mid arm circumference.

It is found that the BMI was significantly lower in our patients with a mean of 19.56%, which was lower when compared to the control population .37.2% of the patients were underweight (<18.5) according to The National Institute Of Health guidelines. This indicates that a significant proportion of our patients are malnourished.

In our study we compared the BMI of the CKD patients to that of the controls. The mean BMI of the study group was 19.56 and that of controls were 23.4. The BMI was significantly lower in the study group

once again reinforcing the fact that protein calorie malnourishment is very common in CKD patients.

Also the mid arm circumference was also significantly lower in our patients (mean of 21.6 cm) It is a crude indicator of somatic protein stores.

The mean hemoglobin in our patients was 7.04 g/dl and the mean GFR was 11.5 ml/mt. Anemia was universal in our study and it showed direct linear relationship with reductions in the GFR. Applying the NKF staging of CKD most of our patients came under stage 4 and 5 who were awaiting some form of renal replacement therapy as the last treatment option

Peripheral smear was done in our patients with the aim to type the anemia .As the conventionally taught normocytic normochromic anemia was found in 30.2 % of the patients and microcytic hypochromic anemia in another 30%, the remainder had dimorphic anemia. This clearly indicates that iron deficiency anemia is a major component in the anemia of chronic kidney disease due to various reasons discussed earlier.

Significant hypoalbuminemia was present in our study with the mean serum albumin level of 3.28g/dl that was significantly lower than the normal controls (p value 0.0001). There was no statistically significant relationship between the GFR and serum albumin and also BMI and serum albumin.

Serum ferritin value was measured in our patients and healthy controls and found to be significantly less in our patients (p value 0.029). There existed no relationship between GFR and serum ferritin. As expected those patients with microcytic hypochromic anemia had a relatively lower serum ferritin when compared to the other types

By applying the NKF guidelines 30 patients out of the total 43 had a serum ferritin below 100ng/ml, which comes to around 69.76% of the patients.

In a similar study by IA Agaba et al have assessed the prevalence of malnutrition in patients with CRF in Nigeria [40]. In this study the BMI was significantly lower than the controls with a mean of 22.4 kg/m2 and low BMI of less than 20 kg/m2 was present in about 21.6% of the patients. In our present study the mean BMI was only 19.56% and proportion of those

who are underweight (< 18.5 kg/m2) were 16 (37.2 %) among the total 43 patients.

The mean serum total protein and albumin were also significantly lower in the patients compared to controls (61.9 +/- 14.4 g/L Vs. 73.8 +/- 6.8 g/L; $p < 0.0001$, and 31.5 +/- 9.3 g/L Vs. 39.6 +/- 4.4 g/L; $p < 0.0001$ respectively) in the Nigerian study

In comparison, our study showed the mean serum albumin was significantly lower when compared to the controls (3.28 +/- 0.41g/dl Vs 4.33+/- 0.25 g/dl; p value 0.0001)

Protein malnutrition (serum albumin < 3.0 g/L) was present in 32 (43.2%) patients with CRF in the Nigerian study and the corresponding value in our study was 13 out of 43 patients (30.2%)

The results of both the studies were very much similar and emphasis should be placed on prevention and/or correction of malnutrition because of its documented adverse effects on the outcomes of maintenance dialysis.

In a study conducted by Mafra D et al with the aim to assess the zinc and iron status in patients with chronic renal failure (CRF) who were not receiving dialysis the serum ferritin and other parameters were assessed among 29 CRF patients. The serum ferritin level was reduced to a mean of 85.5 +/- 67.1 ng/mL. In our study the corresponding values were 77.58 +/- 69.67 among the 43 patients. The results of the two studies were similar.

So every effort should be done to identify and treat the coexistent iron deficiency anemia in patients with chronic kidney disease.

LIMITATIONS OF THE STUDY:

As the study population was small larger studies are required to validate the results of this study.

The protein energy malnutrition in CKD patients should be evaluated using multiple parameters including the SGA(subjective global assessment) ,other serum markers including serum transferrin , pre albumin, IGF-1 etc apart from albumin which was evaluated in our study.

Iron deficiency in CKD should be assessed by using other parameters like transferrin saturation, serum TIBC, newer methods which include soluble transferrin receptors, zinc protoporphyrin and the gold standard method, the bone marrow examination for stainable iron. Here serum ferritin and peripheral smear were the only parameters studied.

Also in our patients the probable causes of iron deficiency like occult GI bleed were not excluded by stool for occult blood or upper GI endoscopy.

SUMMARY

This study was undertaken with the aim to assess the nutritional status in patients with chronic kidney disease who were not on regular dialysis.

A total of 43 patients were included in our study who satisfied the diagnostic criteria of CKD and were evaluated for various parameters like weight, height, BMI, midarm circumference, serum total proteins hemoglobin, peripheral smear and serum ferritin to find out malnutrition and iron status.

For comparison of the results with the general population adequate number of controls were also taken.

A significant proportion of our patients were having protein energy malnutrition as evidenced by the low BMI and very low serum albumin when compared to the normal controls.

Anemia was universal in our population and iron deficiency anemia was a major cause for this in our study as shown by peripheral smear and very low serum ferritin.

CONCLUSION

Protein energy malnutrition was widely prevalent in our population of end stage CKD patients as evidenced by very low serum albumin and BMI.

Profound anemia was universal in our patients, which is an important contributor to the high mortality and morbidity in patients with ESRD

Among the anemic patients, iron deficiency anemia formed a major proportion which has to be corrected by giving iron therapy either oral or by parenteral route before starting on erythropoetin or dialysis therapy.

Applying the NKF guidelines to our population it was found that nearly 70% of the study population didnot have target serum ferritin of 100 ng/ml so it is vital to address this issue of iron deficiency in patients with chronic kidney disease so that necessary investigations can be undertaken to find the cause of iron deficiency if any.

Also adequate supplementation of iron should be given either as oral or parenteral route before initiation of dialysis or erythropoetin therapy to attain the goal according NKF guidelines.

Hypoalbuminemia was also present in a significant proportion of our patients, which is an important predictor of morbidity especially in patients on hemodialysis. In the light of MDRD study it has been shown that a well-designed low protein diet can prevent hypoalbuminemia and its attendant complications.

Eventhough treating the complication of CKD like anemia , PEM etc will reduce the mortality and improve the survival , our ultimate aim should be focused on the preventive strategies for CKD . This include screening high risk population , control of hypertension , DM, limiting the use of nephrotoxic drugs like NSAID'S so that a large section of our population escape the burden of this killer disease

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PROFORMA

NUTRITIONAL ASSESSMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Name: Age: Gender:

Ip no/address: Occupation:

Chief complaints:

Past history:

Duration of illness:

Renal disease: HT: DM: Nephrotic syndrome:

Personal history:

Smoking: Alcohol:

Veg/ non-veg:

Family history:

General Examination:

Pedal edema: Anemia:

Vital data:

PR: BP: RR:

Weight: BSA: Height:

BMI:

GFR:

Mid arm circumference:

INVESTIGATIONS:

Complete Hemogram:

Hemoglobin:
PCV: TC: DC: BT: CT:

Peripheral Smear:

Biochemistry:

Blood sugar:
Blood urea: Serum Creatinine:
Total protein:
Albumin:

Serum ferritin:

Urine examination:

Microscopy:
Albumin: Sugar:
Deposits:

USG abdomen:

K. Dis.No.6807 /E4/1/2007.

Govt. Rajaji Hospital,
Madurai – 625 020. Dt.28.05.2007.

Sub: Establishment – Govt. Rajaji Hospital, Madurai – Ethical Committee Projects approved by the Committee – Intimation – Sent – Reg.

The Ethical Committee of the Govt. Rajaji Hospital, Madurai was held at 12.30 pm. on 28.05.2007 at the Dean's Chamber, Govt. Rajaji Hospital, Madurai, and the following Projects are approved unanimously by the Committee Members.

S.No	Name of Student	Name of the Project approved
01)	Dr.C.Vijay Babu MD PG in General Medicine	Haematological manifestation in HIV patients with and without tuberculosis.
02) ✓	Dr.Aneeb raj. V.P MD PG in General Medicine	Nutritional assessment in patients with chronic kidney disease.
03)	Dr.M.Johnsi rani MD PG in General Medicine	Acute renal failure in Haemotoxic snake envenomation.

Please note that the investigator should adhere the following:-

21) She/He should get a detailed informed consent from the patients/participants and maintain confidentially.
22) She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
23) She/He should inform the Institution Ethical Committee in case of any change of study procedure site and investigation or guide.
24) She/He should not deviate for the area of the work for which applied for Ethical clearance.
25) She/He should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
26) She/He should abide to the rules and regulations of the Institution.
27) She/He should complete the work within the specific period and apply for, if any extension of time is required, She should apply for permission again and do the work.
28) She/He should submit the summary of the work to the Ethical Committee on completion of the work.
29) She/He should not claim any funds from the Institution while doing the work or on completion.
30) She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

28/5/07

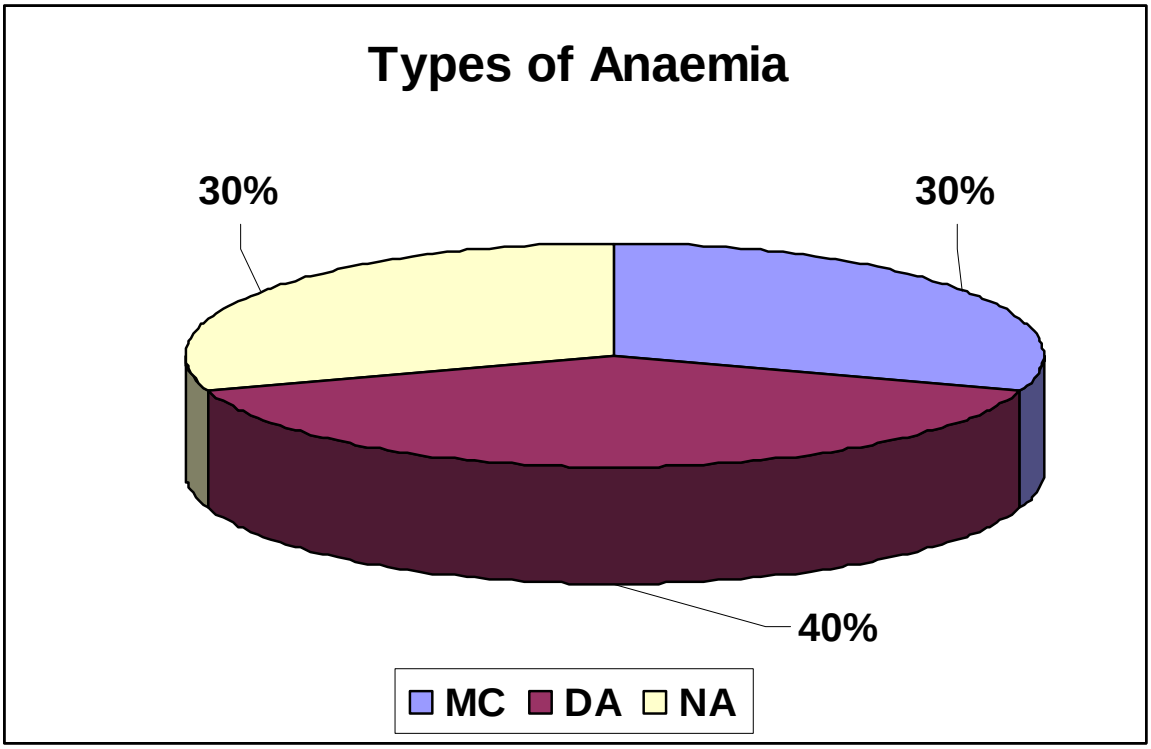
Dean/Chairman,
Ethical Committee, Govt. Rajaji Hospital, Madurai.

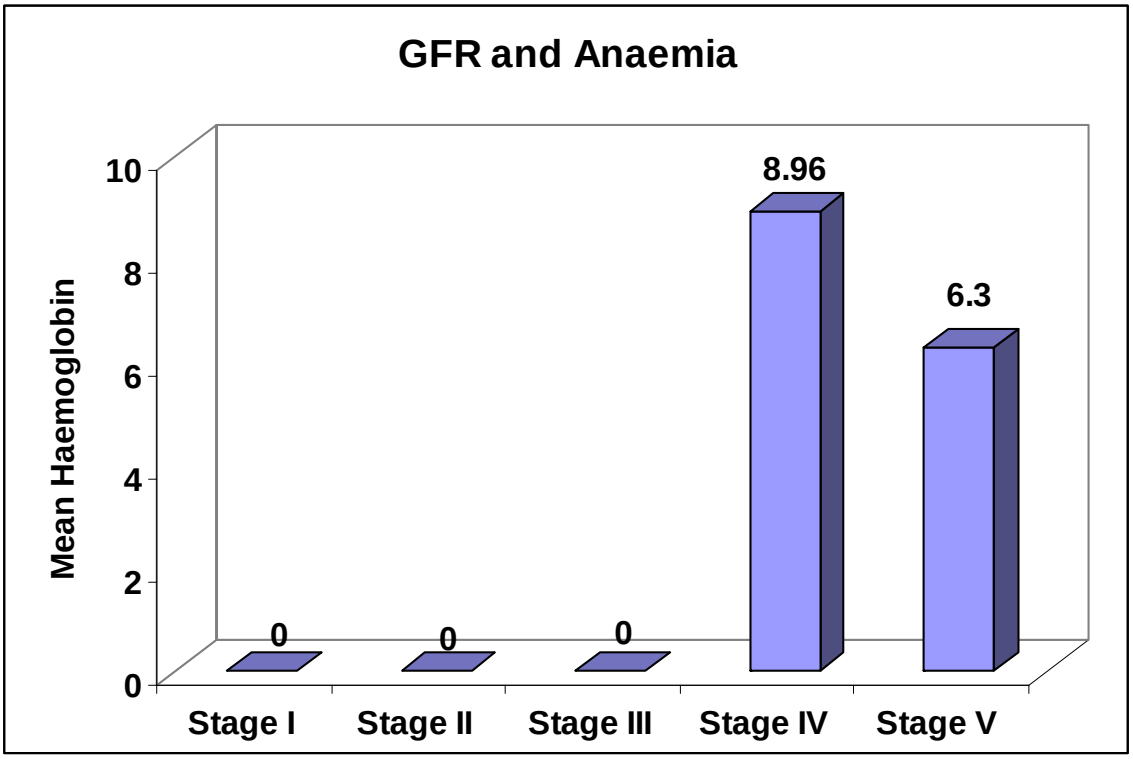
To
The above PG students through the Prof. & HOD of Medicine.

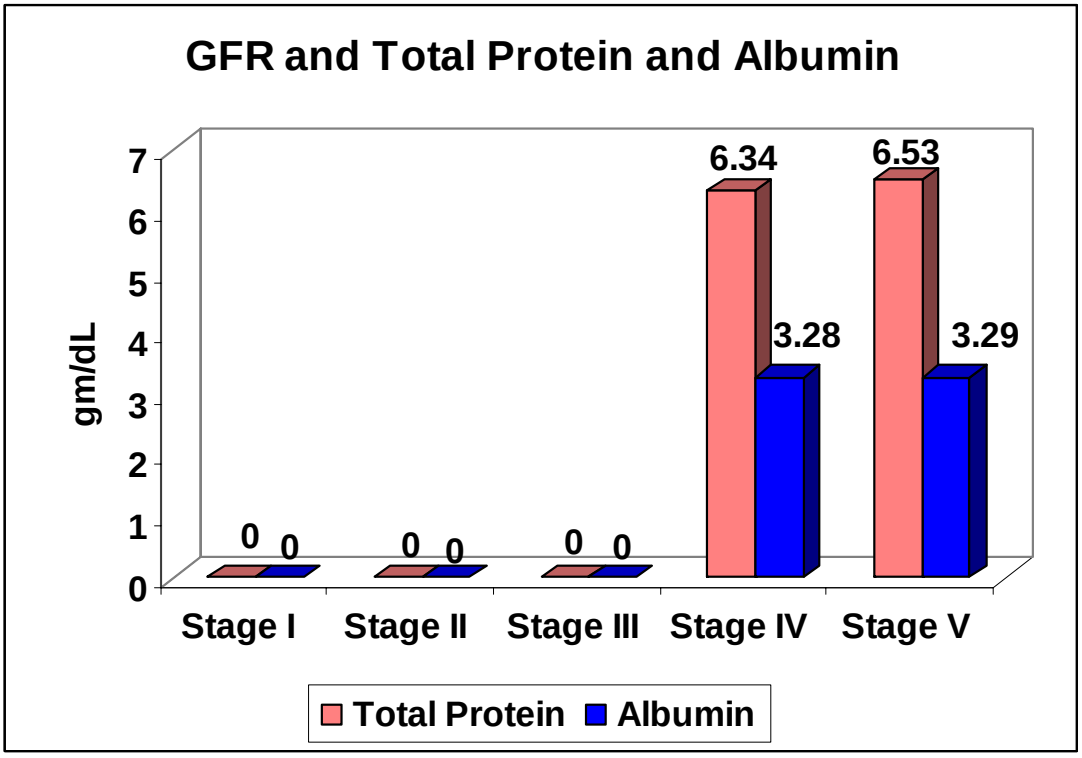
PROFESSOR AND HEAD
DEPARTMENT OF MEDICINE
MADURAI MEDICAL COLLEGE
MADURAI-625 020.

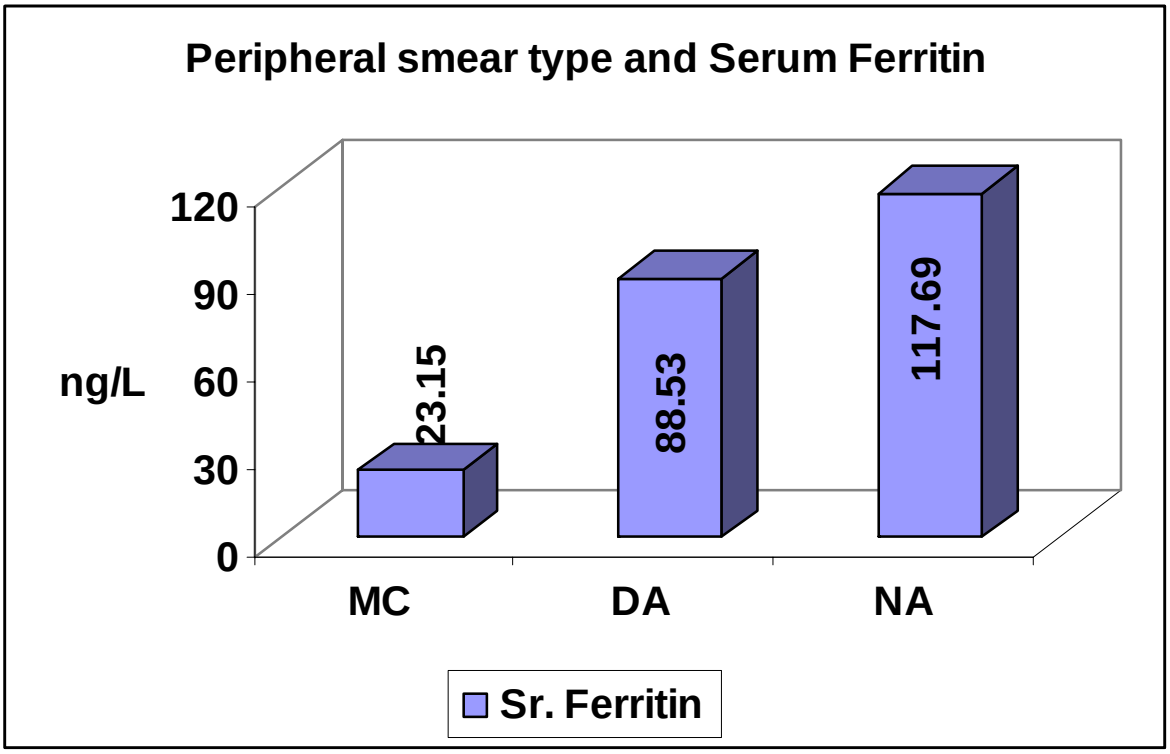
KEY NOTES MASTER CHART

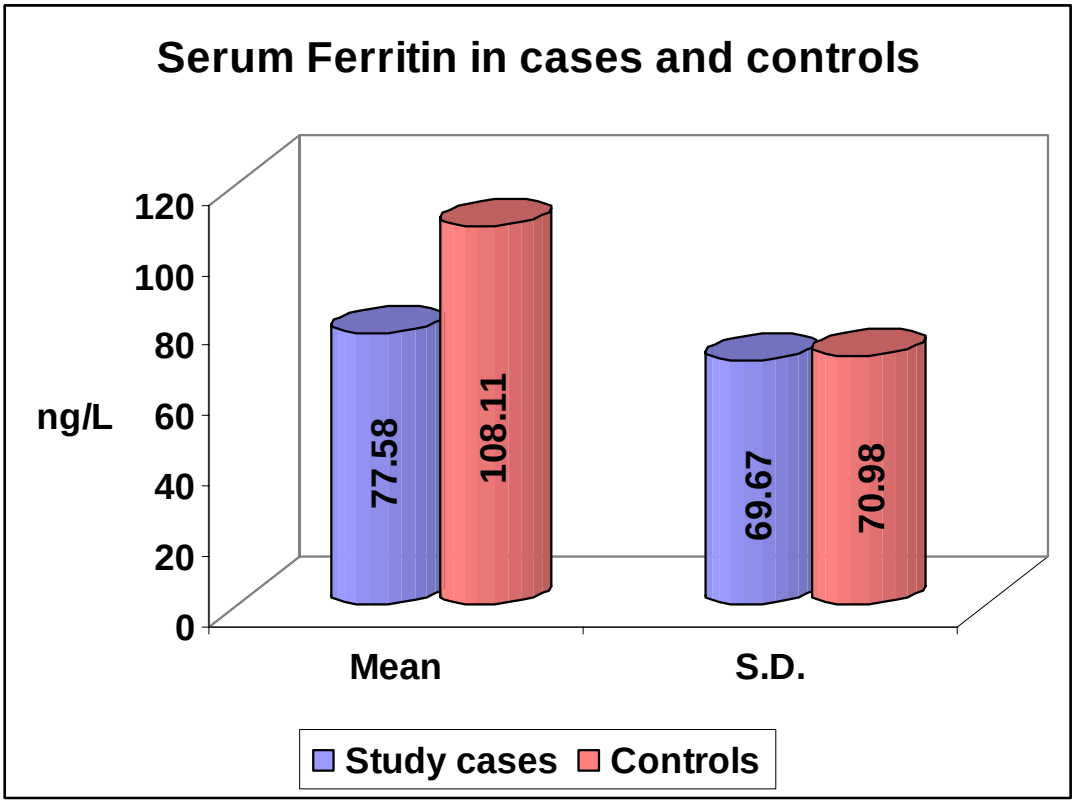
DM	**-**	**Diabetes mellitus**
HT	**-**	**Hypertension**
BP	**-**	**Blood pressure**
WT	**-**	**Weight (kg)**
Ht	**-**	**Height (cm)**
BMI	**-**	**Body mass index**
MAC	**-**	**Mid arm circumference (cm)**
Hb	**-**	**Hemoglobin (g/dl)**
PCV	**-**	**Packed cell volume (%)**
S Cr	**-**	**Serum creatinine (mg/dl)**
B. urea	**-**	**Blood urea (mg/dl)**
T pro	**-**	**Total protein (g/dl)**
S. alb	**-**	**Serum albumin (g/dl)**
LVH	**-**	**Left ventricular hypertrophy**
GFR	**-**	**Glomerular filtration right (ml/mt/1.73m^2)**
SF	**-**	**Serum ferritin (mcg/dl)**

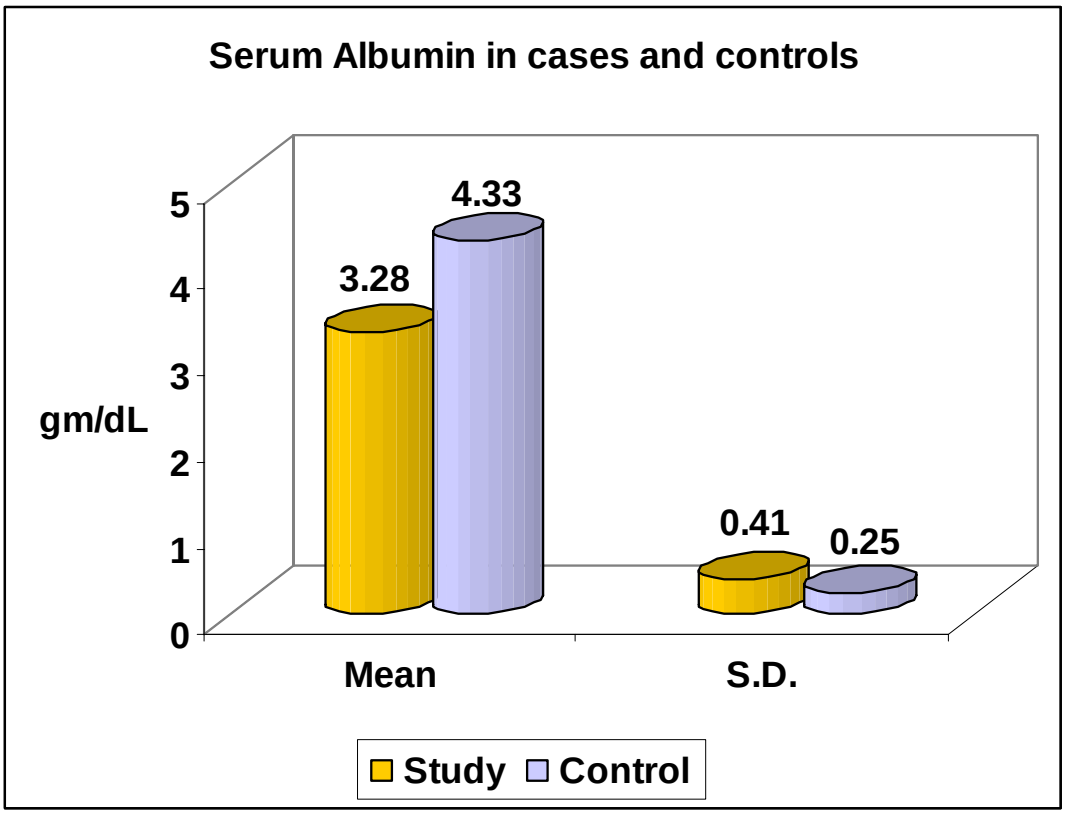

Types of Anaemia
30%
30%
40%
MC
DA
NA

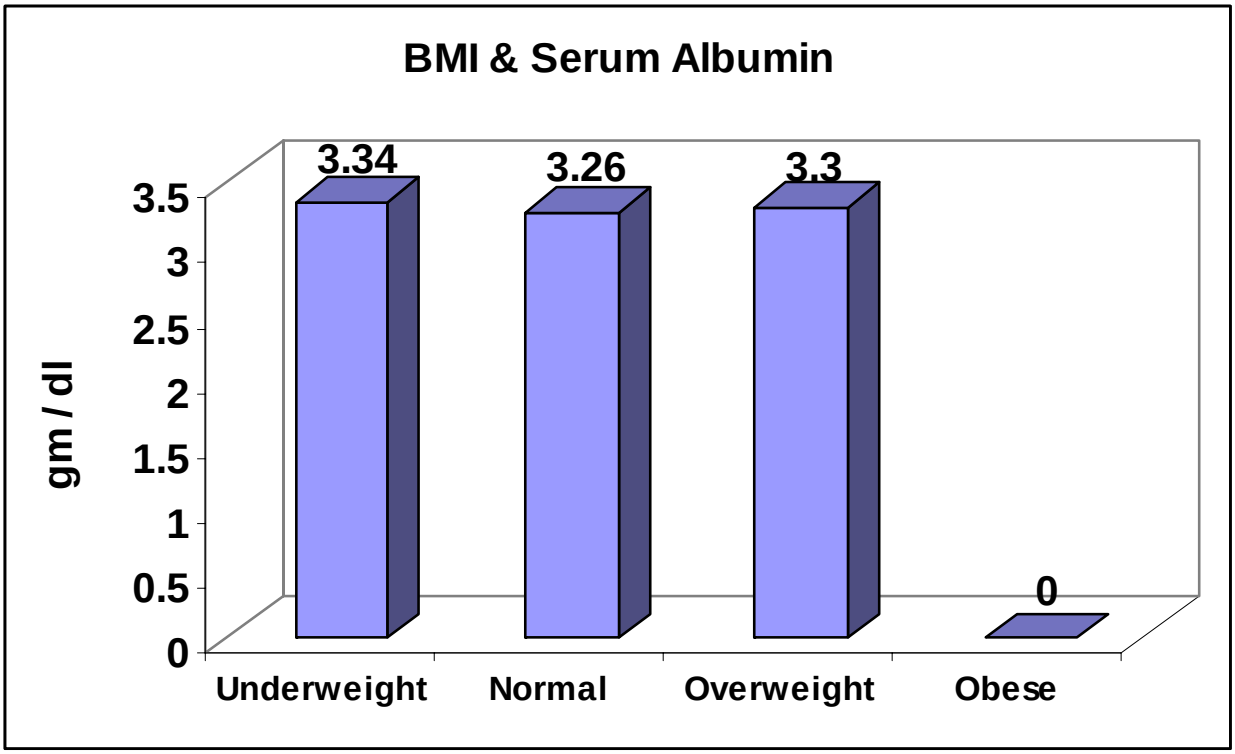

GFR and Anaemia
Mean Haemoglobin
10
8
6
4
2
0
0
0
0
8.96
6.3
Stage I
Stage II
Stage III
Stage IV
Stage V

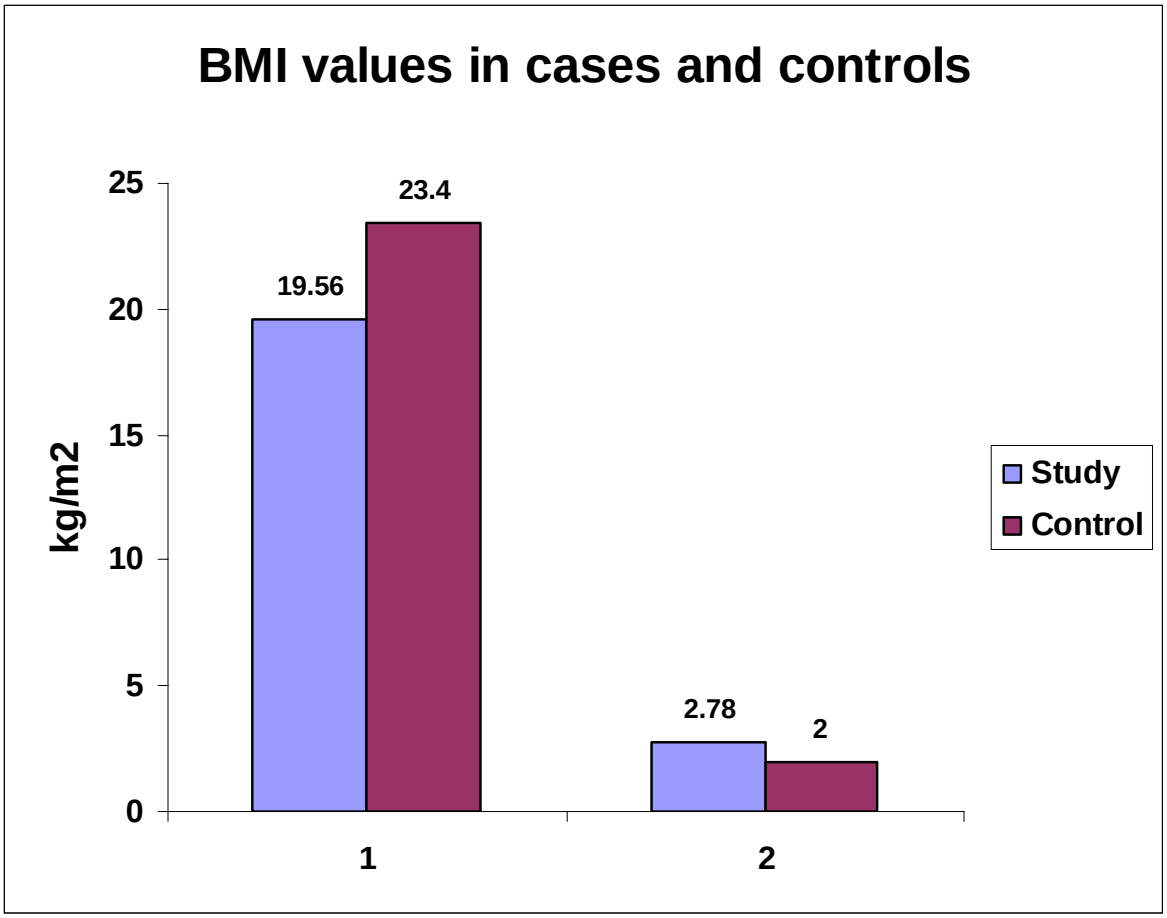

GFR and Total Protein and Albumin
gm/dL
7
6
5
4
3
2
1
0
0
0
0
0
0
0
6.34
3.28
6.53
3.29
Stage I
Stage II
Stage III
Stage IV
Stage V
Total Protein
Albumin

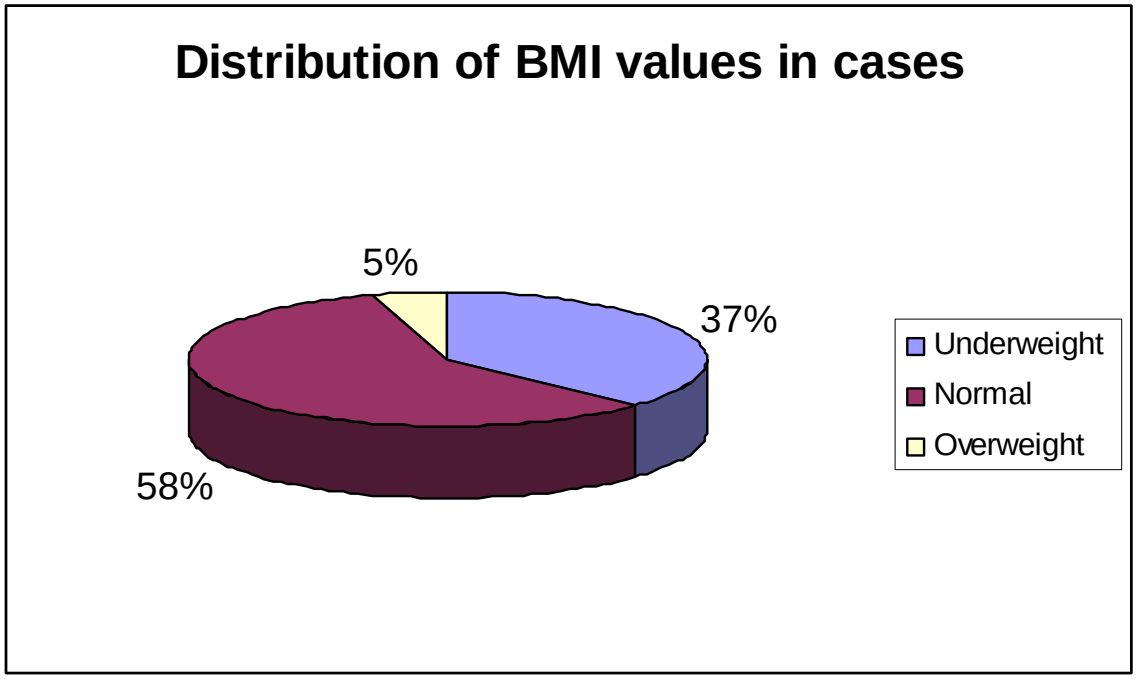

Peripheral smear type and Serum Ferritin
120
90
60
30
0
ng/L
23.15
88.53
117.69
MC
DA
NA
Sr. Ferritin


Serum Ferritin in cases and controls
120
100
80
60
40
20
0
ng/L
77.58
108.11
69.67
70.98
Mean
S.D.
Study cases
Controls


Serum Albumin in cases and controls
gm/dL
5
4
3
2
1
0
3.28
4.33
0.41
0.25
Mean
S.D.
Study
Control


BMI & Serum Albumin
gm / dl
3.5
3
2.5
2
1.5
1
0.5
0
3.34
3.26
3.3
0
Underweight
Normal
Overweight
Obese


BMI values in cases and controls
25
20
15
10
5
0
kg/m2
19.56
23.4
2.78
2
1
2
Study
Control


Distribution of BMI values in cases
5%
37%
58%
Underweight
Normal
Overweight